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Review

Early-Onset Parkinson's Disease: Creating the Right Environment for a Genetic Disorder

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Abstract. Parkinson's disease (PD) by its common understanding is a late-onset sporadic movement disorder. However, there is a need to recognize not only the fact that PD pathogenesis expands beyond (or perhaps to) the brain but also that many early-onset patients develop motor signs before the age of 50 years. Indeed, studies have shown that it is likely the protein aggregation observed in the brains of patients with PD precedes the motor symptoms by perhaps a decade. Studies on early-onset forms of PD have shown it to be a heterogeneous disease with multiple genetic and environmental factors determining risk of different forms of disease. Genetic and neuropathological evidence suggests that there are α-synuclein centric forms (e.g., *SNCA* genomic triplication), and forms that are driven by a breakdown in mitochondrial function and specifically in the process of mitophagy and clearance of damaged mitochondria (e.g., *PARKIN* and *PINK1* recessive loss-of-function mutations). Aligning genetic forms with recognized environmental influences will help better define patients, aid prognosis, and hopefully lead to more accurately targeted clinical trial design. Work is now needed to understand the cross-talk between these two pathomechanisms and determine a sense of independence, it is noted that autopsies studies for both have shown the presence or absence of α-synuclein aggregation. The integration of genetic and environmental data is critical to understand the etiology of early-onset forms of PD and determine how the different pathomechanisms crosstalk.

Keywords: Parkinson's disease, early-onset Parkinson's disease, genetics, environment, risk factors

INTRODUCTION

Classically, Parkinson's disease (PD) is considered a progressive, age-related neurodegenerative disorder of the elderly [1]. While this dogma is driven by the onset of motor symptoms, well-characterized prodromal clinical manifestations can precede motor deficits, and neuropathological protein aggregation

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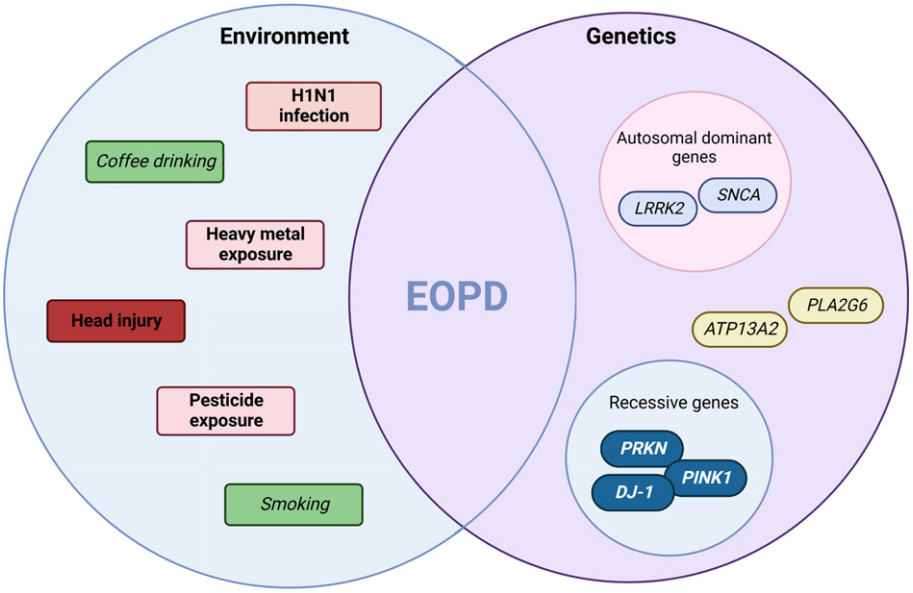

Fig. 1. **Environment and genetic interplay in EOPD**. An interpretation of the multi-hit hypothesis on early-onset Parkinson's disease suggests it is the combination of environmental agents acting on the background of genetic determinants that pre-disposes the individual to disease. Highlighted are both risk (pink-red or bold) and protective (green or italics) factors. This concept in early-onset forms of disease may be due to stronger effects sizes from exposure or higher penetrant genetic mutations observed in specific genes (e.g., *SNCA* or *PRKN*) and molecular pathways (e.g., mitophagy). (Created by BioRender.com)

likely begins decades before the onset of clinical symptoms given recent studies in Alzheimer's disease (AD) and PD [2–4]. With the average age-at-onset of approximately 65 years being based on the appearance of motor symptoms, this raises the interesting question of whether prodromal clinical manifestations and early underlying molecular etiology justify the reclassification of PD as a 'early-onset' disease.

Defining early-onset Parkinson's disease

Early-onset PD (EOPD), sometimes referred to as 'young-onset Parkinson's disease', lacks a consensus definition, but generally refers to patients who develop the classical PD motor symptoms after 21 years old and before 50 years of age [5, 6]. Patients presenting with PD motor symptoms earlier than 21 years old are classified as 'juvenile PD' and usually present with atypical and more severe clinical features [7]. EOPD and juvenile PD cases together comprise between 5-15% of all patients with PD, and are more frequent in males than females (1.5-1.7 : 1) [8, 9]. Age of onset is not the only differential feature between EOPD and the more typical patients with late-onset PD (LOPD; age of onset > 60-65 years) as there are significant differences in disease progression, clinical features, response to medication, and postmortem pathology. Historically, EOPD cases have been reported to be more likely familial (~20-30% of cases are familial) than sporadic LOPD (where 10-15% report family history) [10]. The discovery of novel EOPD genetic and environmental causes and their potential interplay may also still help to further elucidate the pathological mechanisms of the more common late-onset patients with PD. Like typical LOPD, EOPD is clinically and pathobiologically heterogeneous and the most current genetic and environmental etiologies of EOPD will be discussed herein (Fig. 1).

Clinical characteristics and neuropathology of EOPD

It is clear that for PD in general the clinical manifestation of symptoms is heterogeneous, and a number of clinical subtypes have been described [11, 12]. With this in mind, a diagnosis of EOPD is based on the presence of clinical manifestations that define parkinsonism before a predefined age, and it remains unclear whether using age at onset as a cut-off produces a more homogeneous patient group [13, 14]. A number of studies confirm no significant difference for tremor and bradykinesia between EOPD and LOPD; however, EOPD patients are less likely to

present with gait disturbances [15], possibly due to a lower burden of comorbidities affecting gait either due to the younger age of onset, or a slower disease progression. Dystonic posture and post-exercise gait disorders have been reported frequently EOPD as the first symptom [16]. As EOPD and LOPD progress, differences can become more apparent with rigidity, dystonia, dyskinesia, painful cramps, and sexual dysfunctions being more frequent in EOPD than LOPD [17]. By contrast, EOPD patients have a lower risk of developing dementia compared to LOPD patients [17, 18], perhaps again reflecting the general overall health of the individual, e.g., better vascular health and potentially different mechanism of neuropathology progression between EOPD and LOPD. In addition, early studies suggested preservation of cardiac sympathetic innervation in patients with *PRKN*-related disease, these findings have not been observed consistently across EOPD or *PRKN*-patients [19–21].

The reasons for these clinical differences are not entirely clear, but age, environment, or underlying genetic variants likely play important roles. Additionally, diverse distribution of α-synuclein-positive Lewy body (LB) pathology may result in different clinical phenotypes. In LOPD, although remaining controversial, α-synuclein pathology is believed to play an important role in dopaminergic neuronal loss and the subsequent onset and progression of motor symptoms. However, patients diagnosed with EOPD can demonstrate heterogeneous neuropathology, which may or may not include α-synuclein deposits. Specifically, some patients with genetic forms of EOPD harboring familial mutations in *PINK1* or *PARKIN* (*PRKN*) have been shown to mostly lack LB pathology [22–35]. The heterogeneity in α-synuclein pathology raises the question of whether the lack of LB pathology is due to the younger age or whether distinct pathologic mechanisms exist that alter buildup and distribution of the pathology. Interestingly, classical LB pathology in several *PINK1* and *PRKN* cases was observed although confined to the brainstem [31, 36] suggesting the degenerative processes taking place in these forms of parkinsonism may differ from LOPD. The predominant nigral degeneration in the presence of few or no LB deposits led to these cases being defined as "pure nigropathies" with restricted pathology and underlying mitochondrial dysfunction as the primary substrate [37]. This hypothesis is further supported by the known role of environmental toxins (e.g., MPTP) in inducing mitochondrial-related parkinsonism which, together with the sporadic nature of disease, was responsible for PD being described as the archetypal non-genetic disease.

While PD is pathologically defined by the presence of LBs, the biological origin, mechanisms of formation, and role(s) in disease remain unclear to date. Interestingly, recent accumulating data suggest that membranous organelles together with α-synuclein are the main components of LB and that the process of LB formation itself could be one of the main drivers of neurodegeneration, rather than simple α-synuclein fibril formation [38–40]. Of note, alterations in lipid metabolism and trafficking as well as mitochondrial and autophagic-lysosomal function, emerge as common biological pathways that can contribute to LB formation [41], and may provide further links between the various genetic and environmental factors in EOPD and/or LOPD. These studies have raised more questions than answers in regard to whether there are specific subtypes of disease, and whether EOPD represents a distinct entity compared to LOPD.

Environmental determinants

Exposure to environmental agents may modify the risk of developing PD with the same environmental variables affecting LOPD believed to also play a role in EOPD. Studies specifically investigating the association between environmental exposure and EOPD found that only a positive history of head injury seemed to increase the risk of EOPD compared to LOPD [42]. Interestingly, smoking was found to be protective against PD in general with a stronger association with a younger age at onset [43]. Coffee consumption has been reported as possible protective factors in the development of PD; however, the role of coffee intake has not been extensively explored in EOPD yet.

Historically, the H1N1 influenza pandemic of 1917-1918 has been considered a possible environmental cause of parkinsonism. In particular, the development of von Economo encephalitis was directly caused by H1N1 [44]. In addition, results of a study on trends of incidence and birth cohorts of PD reported a slight but significant increase of future risk of PD in men with a date of birth between 1915-1924 [4]. Recently, exposure to H5N1 has been considered a possible PD causative infection in experimental model of PD [45]. It is possible that systemic viral (or potentially bacterial) infection represents the first "hit" of the dual-hit theory of PD [46]. Addi-

tional definitive studies will be needed in the future to explore the role of the current SARS-CoV-2 (COVID-19) pandemic on PD risk although studies have shown that neurodegenerative processes are likely [47–49].

The discovery of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induced parkinsonism dramatically advanced the understanding of the pathophysiology of parkinsonism and increased the understanding of possible risk factors for EOPD [50]. MPTP-induced mitochondrial damage raises the possibility that cases of non-drug induced EOPD have mitochondrial dysfunction as the underlying pathogenesis [51]. On the other hand, in the genetic and non-genetic forms of EOPD, the involvement of environmental agents seems to cause less acute and more long-lasting effect later in life. Paraquat and a number of pesticides have been identified as a risk for PD either as a direct exposure or via polluted water [52, 53]; however, the information on EOPD is limited. Certainly, the duration and amount of exposure has an important weight in the development of PD, together with an individual (genetic) predisposition.

Therefore, in EOPD the environmental risk factors (alone or acting in cluster) may need a stronger individual genetic predisposition to contribute to EOPD. In fact, a study reported an increase risk of developing PD and having a more severe disease in farmers that had head trauma, exposure to pesticides and a genetic susceptibility allele of the *SNCA* REP1 expansion (common variation at the *SNCA* locus is hypothesized to increase expression of α-synuclein protein) but not in farmers with head trauma, exposure to pesticides and no REP1 risk allele [54, 55]. If this is valid for LOPD, we may argue that a stronger individual (genetic) predisposition is needed in EOPD and/or a stronger exposure to environmental risk factors.

ENVIRONMENT-GENE INTERACTIONS

The majority of PD cases are idiopathic, with inherited genetic forms accounting for approximately 10% of PD cases [56]. Many have postulated that PD arises from an interaction between genetic susceptibility and environmental exposures [57]. One of the most studied interactions in PD is between smoking and monoamine oxidase B (MAO-B) enzyme. As noted earlier, smoking has been shown to be protective against PD; however, different polymorphisms in the gene encoding MAO-B may have opposite effects on PD risk in smokers [58]. Another example of gene-environment interaction comes from a genetically predetermined inability to metabolize organophosphates and pesticides that in turn may result in an increased risk of PD [59]. Chronic exposure to rotenone, a mitochondrial complex I inhibitor and pesticide, may alter the genetic expression and production of α-synuclein and DJ-1, leading to PD pathogenesis [60]. In addition, chronic exposure to heavy metals and pesticides is associated with a younger onset of PD [61]. It is also possible that genetic factors only become relevant when placed in the context of an environmental agent and these genes may be more complicated to identify than those that have been identified as monogenic drivers of disease.

Genetics determinants

PD is a genetically heterogeneous disease with family members who carry the same genetic mutation presenting with varying symptomatic manifestation (e.g., age of onset, severity of symptoms, and disease progression rate), suggesting that even less complex Mendelian and monogenic cases of the disease rely on environmental factors or additional genetic modifiers/risks.

Currently, pathogenic variants of variable penetrance have been identified in a handful of genes widely accepted as major determinants or strong risk factors for inherited forms of parkinsonism and PD including *SNCA, PINK1, PRKN, DJ-1*, *LRRK2, VPS35, VPS13C, FBXO7, PLA2G6, SYNJ1, ATP13A2, RAB39B*, and *GBA* [62]. Genes known to cause hereditary ataxias (*ATXN2, ATXN3*, and *FMR1*) and frontotemporal dementia (*C9ORF72, GRN, MAPT*, and *TARDBP)* have also been suggested to influence PD as a secondary phenotype [63]. Additional genes including *UCHL1, HTRA2, GIGYF2, CHCHD2, DNAJC13, TMEM230, LRP10, PODXL*, and *NUS1* have been linked to isolated familial PD cases but are either too rare for proper validation/replication studies or lack definitive evidence of pathogenicity [62–65].

Some genetic mutations are associated with atypical presentations of EOPD, with extrapyramidal symptoms as part of a more complex phenotype. Various forms of variable dystonia-parkinsonism syndromes associated with early onset parkinsonian features have been described; mutations in the *ATP13A2* (PARK9) gene can cause a constellation of symptoms including supranuclear up-gaze palsy, oculogyric dystonic spams, facial-faucial-finger mini-myoclonic and autonomic dysfunction

along with more typical parkinsonian signs and symptoms [66]. Mutations in the *PLA2G6* (PARK14) might be associated with levodopa-responsive EOPD along with marked truncal hypotonia, optic atrophy, cerebellar ataxia and mental retardation [67]. A similar pattern can be observed in those genetic disorders clinically defined as spinocerebellar ataxias (SCA) (e.g., SCA 2, SCA 3, SCA 8, and SCA 17) in which parkinsonism may occur as a prominent sign early in life, and signs of cerebellar dysfunction are the main findings [68, 69]. Genetic forms of EOPD usually show a good response to Levodopa, but a higher risk of developing dyskinesia, with a shorter latency between treatment initiation and motor fluctuations onset [70, 71]. Interestingly, EOPD patients may present a slower disease progression and longer survival compared to LOPD [72, 73].

The identification of genes related to PD has provided useful insights into specific biological pathways involved in PD pathobiology and progression. Mutations in confirmed PD genes mainly alter the dopaminergic neuron maintenance/homeostasis through various mechanisms including, synaptic vesicle protein defects, alterations of mitochondrial quality control, and endosome-autophagy-lysosome dysfunctions [74–76]. For EOPD, two genetic drivers of disease are currently considered: 1) the three recessive genes *PINK1*, *PRKN*, and *DJ-1* and 2) the autosomal dominant genes *SNCA* and *LRRK2*.

SNCA and LRRK2: from early to late, from familial to sporadic

As the presence of LBs is considered the defining pathological confirmation of a PD diagnosis [77], the most relevant genetic cause of EOPD is the highly penetrant mutations observed in the *SNCA* gene encoding α-synuclein. *SNCA* point mutations and genomic multiplications cause autosomal dominantly inherited forms of EOPD with variable penetrance and severity [78]. *SNCA* coding variation is rare and to date only a handful of pathogenic autosomal dominant missense mutations have been discovered along with genomic multiplications of the entire gene [79]. Patients who carry additional copies of the *SNCA* gene (e.g., duplications and triplications) often have an earlier onset and more severe disease phenotypes that appear to be dose-dependent [78]. Interestingly, EOPD patients with the α-synuclein p.A30P substitution have a slightly later disease onset than patients carrying p.A53T, whereas patients with the highly penetrant p.E46K mutation are more likely to develop cognitive symptoms and dementia within two years after the PD diagnosis [80].

The normal function of α-synuclein remains unclear but it is thought to play several roles in synaptic regulation and neurotransmitter release [81]. Pathologically, overexpression of α-synuclein or folding defects/toxic gain of function mutations lead to the accumulation and aggregation of this protein in the pre-synaptic termini of neurons. This leads to a cascade of events that includes neurotransmission inhibition, inhibition of exocytosis, cell stress, and cell death, which then spreads in a prion-like manner through the synaptically connected brain regions at variable rates consistent with Braak staging [82]. However recent links to other genes related to PD also link α-synuclein levels to mitochondrial function (*PINK1* and *PRKN*) and endosomal-lysosomal pathways (*LRRK2*) [74, 75].

Leucine-rich repeat kinase 2 (LRRK2) is a large protein with multiple domains and GTPase and kinase activity that is widely expressed in different tissues [83–85]. Mutations in *LRRK2* are the most common genetic cause of autosomal dominant PD, where the most common disease-causing mutant is likely a gain of function, LRRK2 p.G2019S [86]. Even though *LRRK2* variants are generally associated with LOPD, clinical presentation is heterogeneous with a number of reports of EOPD patients harboring *LRRK2* mutations [87]. The clinical heterogeneity observed seems to be dependent on sex, ethnic background and familial history [88]. Reduced penetrance is becoming a better recognized feature of late-onset complex disease and is likely a combination of risk and protective determinants (both environmental and genetic). Interestingly, large genome-wide association studies have confirmed common risk variants with small effect size in both *SNCA* and *LRRK2* that contribute to overall disease risk of PD [89].

PINK1 and PRKN: regulation of mitochondria quality control

The high energy demand of dopaminergic neurons means a large amount of reactive oxygen species (ROS) is produced in these neurons. As ROS are toxic to mitochondria and to the cell, it is essential that the mitochondrial quality control is efficient in these neurons [75, 90]. Mitochondrial damage and clearance defects are relevant for neurodegenerative disorders in general, and EOPD in particular has been hypothesized to result from a breakdown of these quality control pathways in some cases [91]. This hypothe-

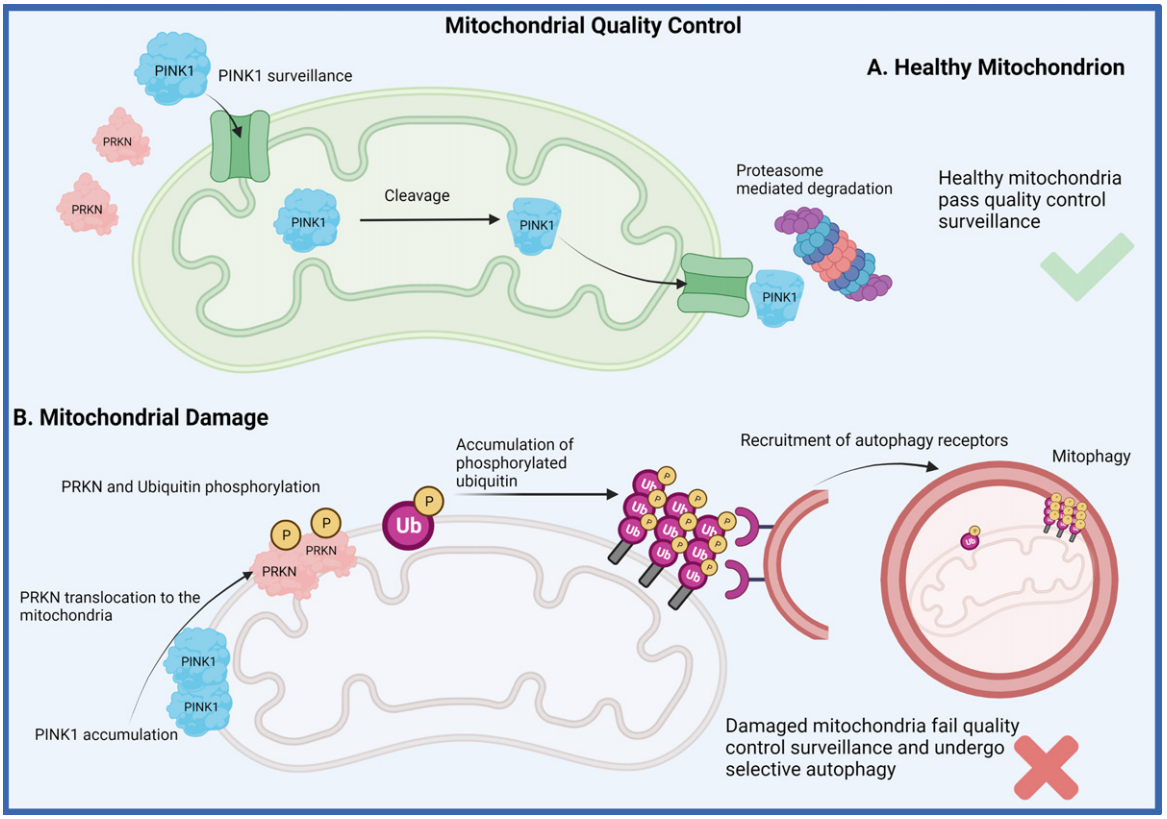

Fig. 2. **Mitophagy pathway.** Two of the genes that have been identified to drive early-onset recessive forms of Parkinson's disease have been demonstrated to play a major role in mitochondrial quality control measures of healthy mitochondria (A). The recessive loss of function for either the PINK1 or "PARKIN (PRKN)" proteins disrupts the normal mitochondrial surveillance process which induces the process of mitophagy for clearance of the damaged organelle (B). This dysfunction is believed to lead to the accumulation of damaged mitochondria eventually resulting in neuronal death. (Created by BioRender.com)

sis is in part driven by the identification of recessive loss-of-function mutations in two genes, *PINK1* and *PRKN* [92, 93], and moreover their functional linkage into a stress-activated mitophagy pathway - the degradation of selectively damaged mitochondria via the autophagy-lysosome system (Fig. 2) [75].

PINK1 is a mitochondrial ubiquitin (Ub) kinase that constantly surveilles organelle health through its regulated import into healthy organelles and rapid cleavage and degradation therefrom. When mitochondrial damage is present though, PINK1 is no longer imported but locally accumulates on the outer mitochondrial membrane where it recruits and activates the E3 Ub ligase PRKN from the cytosol to jointly label and target damaged mitochondria for degradation [75]. *PRKN* encodes for PARKIN, which was first shown to function in the Ub-proteasome degradation pathway in the early 2000 s [94, 95]. Experiments in drosophila were the first to genetically link PINK1 and PARKIN into a linear pathway associated with mitochondrial health and function [96, 97]. Yet, the biological link between PINK1 and PARKIN and their roles in mitophagy were only established later in human cell culture [98–101]. Homozygous loss of function mutations in *PINK1* and *PRKN* cause EOPD, with mutations in *PRKN* representing the most common genetic defect in EOPD patients [93, 102]. Although the symptoms are indistinguishable from sporadic cases, multiple post-mortem brains with *PRKN* mutations do not harbor α-synuclein aggregation and LB pathology [103] and only one report suggests *PINK1*-linked Lewy pathology [31].

The mean age at onset of patients with *PINK1* mutations is 33 years old; however, the onset and severity of the symptoms is highly variable. For example, the youngest patient diagnosed with *PINK1*-related disease was just 5 years old, whereas some *PINK1* patients first present with symptoms at 61 years of age or older [104, 105]. This extreme

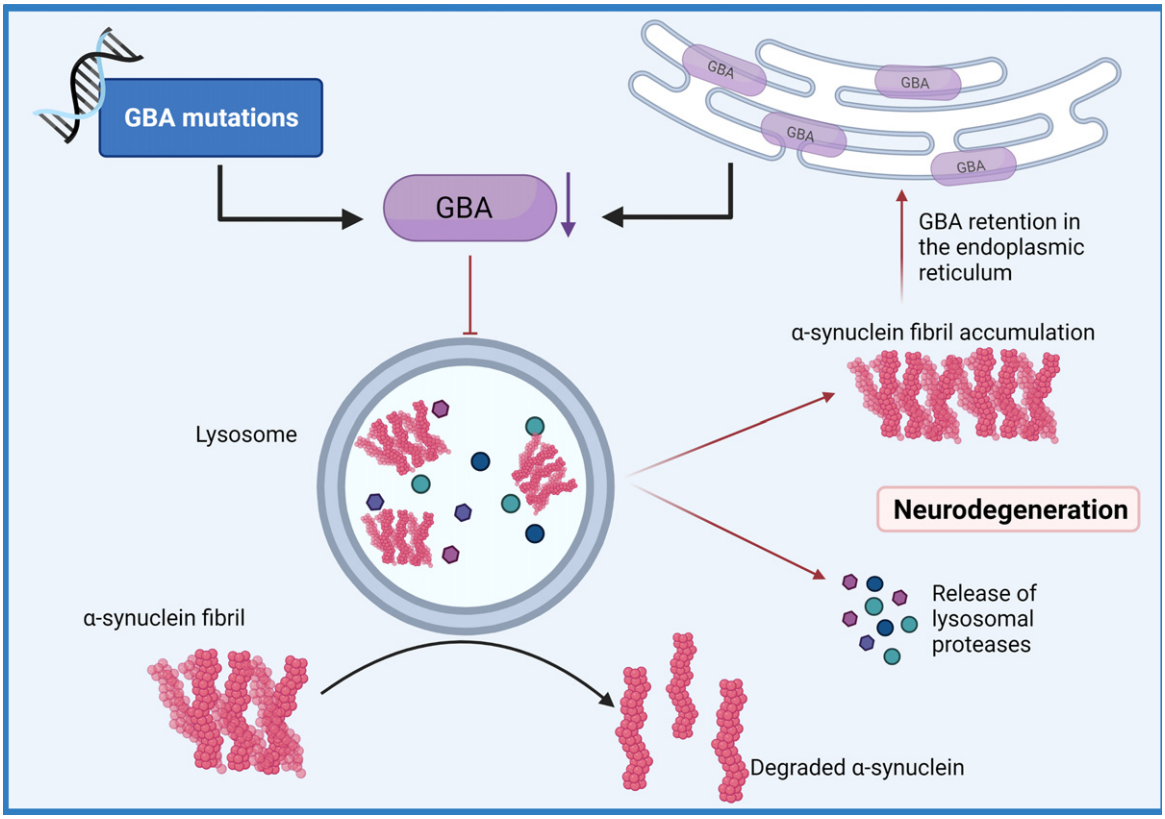

Fig. 3. **GBA-mediated Lysosomal dysfunction.** Mutations of the *GBA* gene that result in haploinsufficiency have been shown to result in loss of lysosomal homeostasis, a reduction of glucocerebrosidase activity, the build-up of lysosomal glucosylceramides and impairs α-synuclein degradation enhancing aggregation. (Created by BioRender.com)

example suggests that there is more to the picture than the *PINK1* loss-of-function variants, with a possibility of population-specific phenotypic expressions of certain gene mutations. However, it is also clear that the extent and duration of mitochondrial stress and damage play critical roles in the activation of the PINK1-PARKIN mitophagy pathway. Moreover, proper flux through the autophagy-lysosome system is crucial for swift and effective degradation and recycling of the mitochondrial cargo.

Interestingly, even though the function of *DJ-1* may not be directly involved in the PINK1-PARKIN mitophagy pathway, there is growing evidence that loss of function variants in *DJ-1* do in fact interact in parallel with the mitophagy pathway during disease progression [106, 107]. *DJ-1* loss of function variants were first described in 2 consanguineous families from geographically isolated regions in the Netherlands and Italy [108], and patients with *DJ-1* loss of function variants are clinically similar to *PINK1-PRKN* patients [109]. Multiple functions have been attributed to *DJ-1* since it was first identified as an oncogene, including as a chaperone with protease activity, a transcriptional regulator, and a role in the maintenance of mitochondrial homeostasis [110]. Most of those functions could not be demonstrated *in vivo* so far, until a recent study in *DJ-1* knock-out rat and mice brains demonstrated that PTEN inhibition and AKT signaling seem to be the main functions of *DJ-1* in the progression of neurodegeneration [107]. AKT signaling promotes the attachment of hexokinase1 and 2 (HK1 and HK2) to the mitochondrial outer membrane, which is an important step that aids the function of the PINK1-PARKIN pathway. *DJ-1* absence in rat and mice brain cells have displayed delocalized HK1 from mitochondria to the cytosol, which in turn may disrupt the efficiency of mitophagy and increase oxidative stress and cell death.

There is controversy whether *PINK1* and *PRKN* deficiency and genetic variation might also contribute to risk for development of PD later in life, so the targeting of this pathway might confer therapeutic value to both EOPD and LOPD [64, 75, 111–114]. With the rise in Next Generation Sequencing and characteriza-

tion of gene expression regulators it will be possible to determine whether EOPD and LOPD patients who carry heterozygous *PINK1-PRKN* deleterious variants also carry additional regulatory variants that could lower the expression efficiency of these proteins under stress. However, it is also becoming clear now that not all mutations are alike and thus genetic and functional analyses must be performed on the single variant level in order to truly determine the pathogenicity [115]. Yet, the amount of mitochondrial damage and the critical threshold functions of PINK1 and PARKIN in that context may also vary from individual to individual and even from cell to cell, further impeding a pure genetic approach.

AGE-AT-ONSET MODIFIERS

Patients with EOPD have considerable age-at-onset (AAO) variation. Genetic variation and sex differences very likely contribute to AAO [116]. Multiple studies have attempted to identify genes or variants that modify the AAO of PD with very little success, likely due to the low sample size of their datasets. The largest aggregate of PD genome wide association studies (GWAS) to date includes a meta-analysis of 17 datasets, with 37,688 PD patients, 18,618 UK Biobank proxy-cases and 1.4 million controls. This study identified 90 independent common genetic risk factors in individuals of European ancestry [89]. Currently, there are efforts to generate a predictive genetic risk score (GRS) that is based on cumulative genetic risk, this may also help determine AAO prediction, as it has been shown that a subset of risk variants overlap with AAO modifiers [117]. A Mendelian randomization portal that uses thousands of GWAS data is now available for the research community in hopes to identify modifiers of disease progression (https://pdgenetics.shinyapps.io/MRportal/) [118].

GBA: lysosomal pathway central in PD pathobiology

Rare coding variants in *GBA* are one the best established risk and AAO modifiers of PD. Homozygous detrimental variants in *GBA* cause Gaucher's disease (GD) which is the most common lysosomal storage disease worldwide [119]. Patients who are heterozygous for GD-causing variants have a 10-30% increased chance of developing PD by 80 years of age; this reflects a 20-fold higher risk compared to the general population [120]. PD patients with *GBA* mutations may exhibit typical manifestations of PD but have a higher risk for dementia with Lewy bodies than patients with LOPD [121]. Patients with homozygotic *GBA* mutations seem to be more susceptible to psychiatric symptoms such as psychosis, hallucinations, depression, anxiety, and apathy, although this has not been confirmed in all clinical studies [120]. Different *GBA* mutations result in different risks of developing PD [122]. It is proposed that patients with known disease-causing variants in other PD genes (e.g., *SNCA*, *LRRK2*, *PINK1*, and *PRKN*) that carry *GBA* mutations may develop an earlier onset and more severe disease [123, 124]. A recent study showed that PD and Lewy body dementia cases with *GBA* variants often carry a substantial number of other PD associated risk variants, which confirms the age of onset modifier hypothesis, and further highlights the importance of the lysosomal pathway in PD pathobiology (Fig. 3) [117, 125]. In addition, heterozygotic carries of *GBA* mutations, may also carry a number of variants of uncertain significance that can further provide heterogeneity to the clinical manifestations, but are likely contributing to the neurometabolic process responsible for the symptoms and disease progression. The interplay between AAO modifier genes with the rest of the genome, epigenome and environmental risk/protective factors is not understood yet, but likely it is one of the major contributors to the endophenotypic variation of LOPD and more specifically to EOPD.

CONCLUSIONS

Over the last two decades it has become clear that up to 10% of patients with EOPD harbor a major genetic determinant [126]. Nonetheless, in most patients, disease cannot be explained by a monogenetic form of inheritance, rather a genetic-environment interaction appears to play a pivotal role in the onset and progression of the disease [57]. GWAS have identified susceptible gene loci for many diseases, including neurodegenerative disorders, however, the variability in common alleles can't explain heritability of common disorders by itself. Moreover, GWAS cannot detect those genes that influence disease onset/progression dependent upon an interaction with other genes or with the environment [127].

Functional analyses of lipid metabolism, mitochondrial health, neurometabolic cellular activity, and autophagic-lysosome capacity will be critical to

place these proposed gene-environment interactions into context. Specific readouts such as phosphorylated ubiquitin, the joint PINK1-PARKIN product and so-called mitophagy tag, may not only be helpful to reveal cross-talk between and potential convergence of PD pathways in cells, tissues, and biofluids, but may also aid in better stratification of patients [128–130]. Likewise, further approaches to identify and compare specific molecular signatures, could be critical to re-categorize forms of PD based on biological pathways, in addition to clinical and pathological definitions, rather than simply age at onset [131].

After the initial discovery of *SNCA* gene mutations as a cause of PD more than 20 years ago, focused research has led to the identification of multiple genes linked to PD onset and progression [132–135]. Gene-environment interactions might be necessary to initiate the cascade of events leading to the onset of PD, and in some cases modify the risk of developing PD as is the case for caffeine exposure and specific polymorphisms that reduce PD risk [136] or smoking and decreased risk of PD that can be reversed in the presence of specific genetic variants [58]. Advances in research and technology have enabled genetic testing to become widely accessible and allowed consumers to access their genetic information without a healthcare professional intermediate. Genetic testing companies such as 23andme empower customers, not only with the ability to access information regarding their ancestry, but also their genetic predisposition to develop certain diseases, or their response to a specific drug, all without having to see a physician. A number of PD risk loci have been identified or confirmed using a genetic database based on the data collected through 23andme DNA samples [137].

A major question that remains unanswered by current genetic-environment studies is whether EOPD and LOPD are distinct disease entities or different staging on the same spectrum of disease. As discussed herein, there are clinical and neuropathologic differences in the phenotypic manifestation of disease signs, but it is not clear whether these are a simply a reflection of overall health (biological age) in the younger patients. Age is recognized as the major risk factor for LOPD, but this is absent in patients with EOPD and may reflect a stronger genetic/environmental component in the latter. However, given the presented genetic and environmental data it may be the scenario whereby there are distinct forms of PD, e.g., α-synuclein-centric versus mitophagy-driven, that may produce/influence both EOPD and LOPD. If this is the case, then whether it is a benefit to split patients by an arbitrary age cut-off is up for debate. What we really need as a field is an unbiased biologic readout that categorizes patients into subtypes and allows a more accurate definition of disease for clinical trial participation. A good example of this is the application of seed assays, such as RT-QuIC (real-time quaking induced conversion), which will facilitate the identification of patients with toxic α-synuclein protein driven forms of disease [138, 139]. Also, the recent work on phospho-ubiquitin (Serine-65) as a marker of mitochondrial health and readout for the mitophagy/mitochondrial quality control pathway, is another example of a potential biologic marker of a specific disease process [128]. Finally, the exposure to toxins may also in part define these subtypes, creating an environment on which the genetic determinants will act to drive phenotypic heterogeneity. Whether we can use these combinations to define specific patients' subtypes, beyond the simple dichotomy of EOPD or LOPD, will be critical for drug development and successful clinical trials. As we start using machine-learning approaches to integrate large scale multimodal datasets, we can perhaps identify these key interactions, tease out cause versus effect questions, and redefine early-onset forms of PD.

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CONFLICT OF INTEREST

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